Section II (Remarks)

A. Summary of Amendment to the Claims

By the present Amendment, Claims 1, 2, 4, 5, 52, and 60 have been amended, and Claim 3 has been cancelled. Claims 1, 5, and 60 have been amended to refer to a dosage range of 0.1 to 0.25 mg, which the Examiner indicated in an Interview Summary dated February 11, 2011 would be allowable.

Although Claims 44-48 have not been amended herein, it is respectfully pointed out to the Examiner that these claims depend, directly or indirectly, from Claim 1, and thus can be properly rejoined, since the composition claim from which these claim depends includes only subject matter indicated by the Examiner as allowable.

Claim 2 has been amended to state a dosage range of from 0.1 to 0.5 mg. Support for 0.5 mg as an endpoint for a dosage range is found in paragraph [0029], so this claim is believed to be fully supported by the specification. As discussed below, this claim is free of the cited reference, Rose, since 0.5 mg is half the lowest dose of 1 mg cited in Rose. At half the lowest disclosed dose, 0.5 mg arguably does not fall within the range of "about 1 mg." Claim 52 has been amended to depend from Claim 2.

Claim 4 has been amended to state a dosage range of from 0.1 to 0.7 mg. Support for the 0.2 to 0.7 mg dosage range is found in paragraph [0006]. As discussed below, this claim is free of the cited reference, Rose, since 0.7 mg is 30 percent lower than the lowest dose of 1 mg cited in Rose. At thirty percent lower than the lowest disclosed dose, 0.7 mg arguably does not fall within the range of "about 1 mg."

The amendments made herein are fully consistent with and supported by the originally-filed disclosure of this application. No new matter within the meaning of 35 U.S.C. §132(a) has been introduced by the foregoing amendments.

B. Interview with the Examiner

Applicants thank the Examiner for the helpful interview held with the Examiner on February 3, 2011. Although agreement was not reached during the interview, Applicants discussed the possibility of amending the claims to a dosage range of 0.2 to

0.8 mg, which arguably falls below the dosage range in Rose, or, alternatively, the possibility of amending the claims to claim a dosage range of 0.2 to 0.7 mg.

Following the helpful interview, the Examiner confirmed that a different dosage range, 0.1 to 0.25 mg, would be patentable. Applicants have amended several of the claims to include this patentable dosage range, so that even if the arguments presented herein with respect to other claims are not persuasive, the next Office Action will include an indication of allowable subject matter.

The Examiner is encouraged to consider the additional amendments and arguments, and if they are not considered persuasive, to contact the undersigned Applicants' representative to discuss possible further amendments and/or cancellation of rejected claims to facilitate allowance.

C. Rejections under 35 U.S.C. 103 (a)

Claims 1-5, 49, 52-57, and 59-61 were rejected under 35 U.S.C. 103 (a) as obvious over U.S. Patent No. 6,316,433 to Rose ("Rose") in view of Remington's Pharmaceutical Sciences and U.S. Patent No. to 4,983,602 to Yamane ("Yamane"). Claim 3 has been cancelled, thus mooting the rejection of this claim.

Claims 1, 5, and 60 (and Withdrawn Claims 44-48)

These claims have been amended in a manner consistent with the interview summary, to claim subject matter indicated as allowable by the Examiner. Because these claims are in condition for allowance, they are not discussed further below with respect to the obviousness rejection.

Withdrawn Claims 44-48 also depend from Claim 1, so are also allowable, if the Examiner will favorably consider rejoining these claims.

Non-Obviousness of Claims 2, 4, and 52

Claim 2 as amended relates to a pharmaceutical composition comprising a unit dosage form of rifalazil in an amount between 0.1 and 0.5 mg. Claim 52 depends from Claim 2.

Claim 4 as amended relates to a pharmaceutical composition comprising a unit dosage form of rifalazil in an amount between 0.1 and 0.7 mg.

It is believed that these dosage ranges are far enough below the "about 1mg" range disclosed in Rose.

Rose

The mention of "about 1 mg" appears in Rose in Claim 1, which refers to "[a] method for treatment of bacterial infections caused by Mycobacterium tuberculosis, Mycobacterium avium complex, Chlamydia pneumoniae or Helicobacter pylori in human subjects by once-a-week or twice-a-week administration of rifalazil in a dosage from about 1 to about 100 mg."

While the Examiner also cites to the Abstract and claims 11 and 16 as teaching "about 1 mg," respectfully, the Abstract and Claim 11 refer to 1 mg, not "about 1 mg," and Claim 16 depends on Claim 14, which depends on Claim 1. So, Claim 1 is the only mention in Rose of "about 1 mg," and it is in the context of the range "about 1 to about 100 mg."

In terms of obviousness, it would arguably not be obvious to provide a dosage range half that of the lowest number provided, and 0.5% of the highest number provided. It is important to look at the context of the patent in determining the meaning of the term "about."

In Figure 1, Rose discloses a series of experiments *in human volunteers*, in which daily dosages of 5 or 25 mg resulted in a decrease in white blood cell counts. In Figure 2, the chart showed the results when the daily dose was 25 mg, and in Figure 3, when the daily dose was 5 mg.

In Figure 4, Rose showed the changes in absolute neutrophil count in daily dosing regimens where the daily dose was 5 or 25 mg compared to a control group. Figure 5 shows the effect of a daily dose of 25 mg, and Figure 6 shows the results when the daily dose was 5 mg.

In Figure 7, Rose shows the changes in platelets counts after 20 daily administration of 5 and 25 mg rifalazil to healthy volunteers, compared to a control group receiving placebo.

Importantly, these results were used to show why daily administration of these dosage ranges **should not be performed**.

Rose then provides Figures 8, 9, and 10 to show that a once a week dose of 25 or 50 mg for five weeks did not have the same negative effect on white blood cell counts, neutrophil counts, or platelet counts.

So, while Rose includes a claim to "about 1 to about 100 mg" once or twice a week, the actual administered doses in this dosing regimen were significantly higher than 1 mg – they were either 25 mg or 50 mg, once a week. Accordingly, reading the "about 1 to about 100 mg in the context of the full patent specification, rather than in a vacuum, one can see that dosages significantly lower than 1 mg (i.e., 30% or 50% lower) than the lowest dosage range in Rose, and very much lower than the dosage ranges Rose actually tested in support of the once or twice a week therapy.

Analysis

Rose teaches relatively high doses, given once or twice a week, to overcome the limitations (decreased white blood cell, neutrophil, and platelet counts) associated with daily administration of rifalazil.

The claimed invention overcomes the same limitations by administering a significantly lower dose. Though not required by Claims 2, 4, and 52, these dosage ranges are intended for daily administration. While the intended use of a composition typically does not impart patentability to a composition, it is submitted that knowledge of how the composition is to be used is relevant to helping explain how the instant solution to the problem (decreased white blood cell, neutrophil, and platelet counts) is patentably distinct from the solution to the same problem as disclosed by Rose.

For this reason, Applicants respectfully assert that Claims 2, 4, and 52 are non-obvious over Rose.

Applicants understand that Remington and Yamane are also cited. Respectfully, the Examiner does not discuss how Yamane is being used in the rejection (i.e., the only mention of Yamane in the Office Action is in the rejection itself.

A careful review of Yamane reveals that it teaches a unit dose ranging from 1 mg to 5g:

> The antibacterial agent of the present invention is administered in such a dose that the desired activity is achieved without any side-effect. Though the actual dose should be determined according to the judgement of the doctor, a usual dosage is about 10 mg to about 10 g, preferably about 20 mg to about 5 g, on the basis of the rifamycin derivative (I) per day for adults. The antibacterial agent of the present invention can be used in a pharmaceutical dosage unit containing **1 mg to 5 g, preferably 3 mg to 1 g** of an effective component.

As such, Yamane is less relevant than Rose (which was cited for its teaching of "about 1 mg," rather than "1 mg."

Further, Remington is cited for the limited purpose of purportedly teaching the use of "loading" dosages.

Such loading dosages are not present in Claims 2, 4, and 52, so it is believed that Yamane and Remington do not overcome the deficiencies of Rose, so the obviousness rejection of these claims should be withdrawn.

Rejection of Claim 49

Claim 49 relates to pharmaceutical formulations comprising rifalazil that include a loading dose regimen. The compositions include two different dosage units, a first dosage unit comprising rifalazil and a second dosage unit comprising a smaller dose of rifalazil than said first dosage unit. The second dosage unit comprises between 0.1 and 5.0 mg of rifalazil.

The Examiner indicates that instructions for the administration of a first dosage unit before a second dosage unit are insufficient to impart patentability. However, the

presence of the loading dose and the lower sustained dose are sufficient to overcome the cited references.

Rationale for Using the Loading Dose and Lower Sustained Dose

Paragraph [0016] of the instant application teaches the following:

> [0016] In one preferred method of carrying out the foregoing method, the antibiotic that is effective against the multiplying form of the bacterium is administered in an amount and for a duration to reduce the number of bacteria in the patient to less than about 10^6 organisms/mL. This typically takes from a few hours to one, two or three days, but may take as long as a week. After this has been achieved, the patient is then administered a unit dosage form, low-dosage regimen, or loading-dose regimen of rifalazil described herein in an amount and for a duration effective to complete the treatment of the patient. Antibiotics that are effective against the multiplying form of the bacterium include any of the antibiotics described herein.

Respectfully, Remington's does not discuss the unique problems associated with bacteria that have both a multiplying form and a non-multiplying form. This type of bacteria is particularly difficult to treat. One has to first treat the active bacterial infection, and subsequently ensure that any bacteria that are non-multiplying when the antibiotic is first administered are killed when they start to multiply.

Most antibiotics are incapable of killing bacteria when they are in their non-multiplying form. A higher dosage of rifalazil, used to kill the multiplying form of the bacteria during an active infection is safe, but it is not desired to sustain this dosage to kill remaining bacteria as they transition from the non-multiplying form to the multiplying form. Such a sustained high dosage could result in undesired side effects. However, due to the persistence of rifalazil in the blood stream (i.e., a relatively long circulating half-life), and the relatively low number of bacteria that emerge at any given time, following the effective treatment of the multiplying form of the bacteria with the first dosage, Applicants have determined that a sustained lower dosage is sufficient to treat the

infection until the body is cleared of the initial multiplying form, and (later on) the non-multiplying form as it transitions to a multiplying form.

As the only mention of a loading dose regimen is apparently from Remington's, and does not relate to either rifalazil or to the treatment of bacteria with multiplying and non-multiplying forms, the claimed subject matter is not obvious in view of this combination of references.

Further, the actual once/twice weekly dosages administered to patients in Rose were 25 or 50 mg. The once daily dosages were 5 or 25 mg, and were indicated as causing significant side effects (reduced white blood cells, neutrophils, and platelets). The claimed invention uses a lower dose that is below the daily dosages shown by Rose to be problematic, while at the same time providing a therapy that is effective at treating both the multiplying and non-multiplying forms of the bacterial infection. This provides yet another reason why the claimed subject matter is non-obvious over Rose.

Rejection of Claim 53 and dependent claims thereof

Claim 53 relates to a composition of rifalazil, in unit dosage form, wherein each dose is in the range of between 0.1 and 5 mg, where the composition includes instructions for administration on a daily basis for a period of time of at least two consecutive days.

Claims 54-57 refer to the daily administration for a period of at least 5, 10, or 30 days, or between 4 and 14 days, respectively.

Claim 59 refers to the administration of between 0.1 and 3 mg/day.

Again, Rose refers to the once or twice weekly administration of between 1 and 100 mg/rifalazil. Applicants have discovered that daily administration of between 0.1 and 5 mg overcomes the side effects observed by Rose associated with daily administration of rifalazil.

Applicants understand that the Examiner has expressed an unwillingness to consider instructions for daily administration as imparting patentability. However, in light of the foregoing, if she were to consider instructions as a part of the composition, it would arguably be clear that the daily administration of a dosage lower than that which

causes side effects is patentably distinct from the once or twice weekly dosage of the same dosage range that caused side effects when delivered daily. *(The preceding sentence mentions the "same dosage range," though, in the light most favorable to the Examiner's obviousness rejection, one would properly characterize this as an overlapping range, because the exemplified dosages (25 and 50 mg, once or twice a week) are significantly higher than the lower range disclosed as providing side effects 5 mg/day.))*

As there is a clear and patentable distinction between what is claimed, and what is disclosed in the art cited by the Examiner, the Examiner is encouraged to either allow the claims in the current form, or to suggest a form that would be sufficient to cover this patentable treatment regimen. One possible amendment is discussed below.

Applicant understands that claims to methods of treatment have been restricted out (hence, the withdrawal of Claims 44-48), but the main purpose of a restriction requirement is to reduce the burden on the Examiner. Respectfully, the Examiner has already performed a search that would have encompassed methods of treating bacterial infections by administering low doses of rifalazil on a daily basis. She has identified what she believed to be the closest art, namely, a reference teaching that the problems associated with the daily administration of a particular dosage of rifalazil can be overcome, and antimicrobial efficacy maintained, by switching to a once or twice-weekly dosage. Arguably, a method of overcoming these problems by administering a lower daily dose, to overcome the same problems, is a completely separate and patentably distinct approach.

The Examiner has already considered these arguments, and performed her search. It should be a simple matter to take the "instructions for daily use" language, and convert it to a method step (i.e., wherein the composition is administered for a series of successive days), and convert these composition claims to method of treatment claims. Doing so would be a much more efficient use of U.S. Patent and Trademark Office resources than requiring Applicants to pursue this (already searched) subject matter in a divisional application, and such would be greatly appreciated by Applicants.

Applicants hereby authorize the Examiner to prepare an Examiner's amendment to this effect, if such would result in allowance of these claims, or, alternatively, invite the Examiner to contact the undersigned Applicants' representative to prepare a Supplemental Amendment if she agrees that doing so would result in allowable subject matter, but otherwise goes beyond the purview of what she can do in an Examiner's amendment.

CONCLUSION

As amended, Applicants respectfully assert that all pending composition claims are patentably distinguished over the art, and are in form and condition for allowance. The Examiner is encouraged to favorably consider rejoining one or more method claims, as they have been amended to include the limitations of composition claims indicated in an Interview Summary as being allowable.

Should the Examiner still consider Claims 53 and dependent claims thereof to be obvious, but be willing to consider entry of method of treatment claims, she is respectfully requested to prepare an Examiner's amendment, or to contact the undersigned Applicants' representative to suggest the submission of a Supplemental Amendment converting these claims to method of treatment claims.

Should the Examiner not be inclined to permit rejoinder of one or more of the method claims, and/or to favorably consider Claims 53 and dependent claims thereof in their present form or as amended to be in the form of method claims, she is encouraged to contact the undersigned Applicants' representative to authorize an Examiner's amendment to cancel these claims in order to facilitate issuance of a Notice of Allowance.

Respectfully submitted,

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